

REMARKS

1. Status of the Claims

In the Advisory Action dated September 4, 2003, the Examiner has indicated that Applicants' response filed on August 8, 2003 had been considered but did not place the case in condition for allowance. Claims 1, 3, 5, 8-12, 17-24, 28, 57 and 58 stand rejected for lack of enablement.

2. Claim Rejections under 35 U.S.C. §112

The Examiner has again rejected claims 1, 3, 5, 8-12, 17-24, 28 and 57-58 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The Examiner indicates that Applicants' prior response and the Declaration of Dr. Hertz have been considered but are not sufficient to overcome the enablement rejection. The Examiner's remarks are set forth on page 2 of the Advisory Action. Specifically, the Examiner states that the Declaration of Dr. Hertz submitted with Applicants' last response was insufficient to overcome the rejection because the Declaration was not (1) commensurate in scope with the claims and (2) did not present any evidence relating to the down-regulation of OPGL activity. Applicants respectfully disagree and submit that the Declaration of Dr. Hertz demonstrates that the administration of a modified OPGL polypeptide as recited in the claims will result in the down-regulation of OPGL activity in animal. Applicants address each of these points in more detail below.

The Examiner has argued that the evidence and data described in the Declaration are not commensurate in scope with the present claims. The Examiner summarizes the Declaration as being drawn to evidence surrounding the use of RANKL AutoVacTM to produce antibodies and for a method of reducing bone loss in post-menopause (ovariectomy) and rheumatoid arthritis

mouse models and concludes that the RANKL AutoVac construct and the method of reducing bone loss are not commensurate in scope with the “modified OPGL” or the method recited in the claims. Applicants respectfully disagree. The first paragraph of the Hertz Declaration clearly indicates that the Declaration was submitted to establish that administration of a vaccine against OPGL (also referred to as RANKL in the Declaration) can be used to treat diseases characterized by excessive bone loss. This is because administration of the RANKL AutoVac construct to the animal results in the production of antibodies against the animal’s own OPGL. Thus, the *in vivo* activity of OPGL in the animal is down-regulated. The RANKL AutoVac constructs described in the Hertz Declaration fall within the scope of the modified OPGL polypeptides according to general formula I recited in the instant claims. Accordingly, Applicants submit that the evidence summarized in the Hertz Declaration regarding production of an anti-OPGL response in response to vaccination with the RANKL AutoVac construct is directly applicable to the presently claimed invention and can be relied upon to establish that the presently claimed invention will work for its intended purpose.

The present claims are directed to a method of down-regulating the *in vivo* activity of the osteoprotegerin ligand (OPGL) in an animal by administering an immunologically effective amount of a modified OPGL polypeptide having general formula (I). The RANKL AutoVac constructs described in the first paragraph on page 3 of the Hertz Declaration were designed by incorporating promiscuous T helper cell epitopes into the polypeptide. These constructs would fall within the scope of the “modified OPGL polypeptides” recited with the claims because as described on page 18 of the Specification, the “MOD” substituents in formula I can be (or contribute to) T helper epitopes of foreign origin (either by including a complete foreign epitope or by providing a stretch of amino acids which are identical to a foreign T helper cell epitope). A person of ordinary skill in the art would readily appreciate that evidence in the Hertz Declaration regarding the generation of antibodies against the animal’s own OPGL in response to vaccination with the RANKL AutoVac constructs are equally applicable to the present invention. That is to say that immunization with the modified OPGL polypeptides according to the claims would also have the same effect. Thus, Applicants submit that the Hertz Declaration evidence is commensurate in scope with the present claims.

Next, the Examiner appears to argue that the Declaration fails to establish that vaccination with RANKL AutoVac results in the down-regulation of OPGL activity. The Examiner admits that the Declaration provides evidence that the use of the RANKL AutoVac constructs can be used to decrease bone loss. However, the Examiner argues that Applicants have failed to establish a nexus between the decrease in bone loss with a “down-regulation of OPGL”. Applicants disagree. Applicants believe that the Declaration establishes that immunization with the vaccine constructs will produce the desired immunogenic response. The two experiments summarized on page 3 of the Declaration demonstrate that immunization with the RANKL AutoVac vaccines produced a rapid and sustainable generation of polyclonal anti-RANKL antibodies that effectively cross-react with native non-modified native mouse RANKL. This is precisely the goal of the present invention. A person of ordinary skill in the art could reasonably conclude that administering modified OPGL polypeptides according to the present invention would similarly result in the generation of antibodies against the animal’s native non-modified OPGL and thus down-regulate the *in vivo* activity of the OPGL protein.

The Declaration also summarizes the results of two bone resorption studies wherein administration of the RANKL AutoVac constructs was found to (1) protect mice from ovariectomy induced loss of bone mineral density in the post-menopausal osteoporosis mouse study and (2) reduce the recruitment of activated osteoclasts to the joints, reduce synovial inflammation and reduce bone destruction in the rheumatoid arthritis mouse study. The role of OPGL in the development of Osteoporosis and other diseases characterized by the continued loss of bone tissue is discussed in the Specification (see pages 1-4). To briefly summarize, OPGL is a potent osteoclast differentiation factor when combined with CSF-1 and is also a potent activator of mature osteoclasts, the primary bone resorption cells (see page 6). The inventors believed that many diseases characterized by an excess rate of bone resorption could be treated by down-regulating osteoclast differentiation/maturation/formation and osteoclast activation through the *in vivo* production of antibodies capable of neutralizing OPGL (see page 8). The Declaration evidence, as acknowledged by the Examiner, demonstrates that the RANKL AutoVac constructs produce antibodies against the animal’s native non-modified OPGL and reduce bone loss. Applicants submit that a person of ordinary skill in the art would readily recognize the correlation or nexus between the reduction in bone loss and the down-regulation of

OPGL activity based on the teachings of the Specification. The Specification outlines the role of OPGL in osteoclast formation, differentiation and activation. Administering a vaccine which produces antibodies against the animal's own OPGL protein will necessarily disrupt these activities. This is corroborated by the data presented in the Declaration wherein a reduction in e.g., bone resorption and recruitment of activated osteoclasts was observed in the two mouse studies.

The present invention provides a method for down-regulating OPGL activity by enabling the production of antibodies against OPGL. The data presented in the Hertz Declaration clearly demonstrates that administration of the RANKL AutoVac constructs results in the production of antibodies against the animal's native non-modified OPGL. The therapeutic effects of the down-regulation of OPGL activity are confirmed by the results of the two mouse model studies. As discussed above, the RANKL AutoVac constructs fall within the definition of the modified OPGL polypeptides according to the present invention and as such, Applicants submit that a person of ordinary skill in the art would expect that vaccination with the claimed constructs would also lead to the down regulation of OPGL activity in the subject. Accordingly, reconsideration and removal the enablement rejection is respectfully requested.

Favorable consideration and early allowance of the claims is requested.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at 714-708-8555 in Costa Mesa, CA.

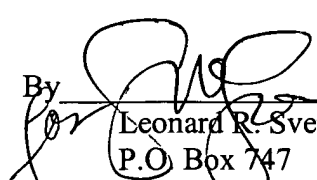
Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for an extension of three (3) months to November 8, 2003 for the period in which to file a response to the Office Action dated May 8, 2003.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,


BIRCH, STEWART, KOLASCH & BIRCH, LLP

LRS/KR/sml
4614-0105P

By  # 47,604
Leonard R. Svensson, #30,330
P.O. Box 747
Falls Church, VA 22040-0747
(714) 708-8555

hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: Nov 10 2003
(Date of Deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP


(Signature)
Nov. 10, 2003
(Date of Signature)